REMARKS

This application has been reviewed in light of the Office Action dated October 28, 2008. Claims 1 and 3-18 are presented for examination. Claim 2 has been cancelled, without prejudice or disclaimer of subject matter and its recitations incorporated into Claim 1. Claims 3-7, 9 and 15 have been amended as to matters of form only, to ensure consistency of terminology, and/or correct claim dependency. No change in scope is either intended or believed effected by at least these latter changes. Entry of the present amendments and favorable reconsideration is requested.

The Examiner has objected to Claim 15 due to the inconsistent use of comma's and semi-colon's. As suggested by the Examiner, Claim 15 has been amended to overcome the objection.

Claims 1, 13 and 17 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 3,993,072 (Zaffaroni). The limitations of Claim 2 have been incorporated into Claim 1. Accordingly, this change obviates the anticipation rejection based on Zaffaroni.

Claims 1, 3, 6-8, 13-15 and 17 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 3,977,404 (Theeuwes), in view of Zaffaroni.

Theeuwes concerns itself with osmotic devices, as is evident from, for example, the title and the opening paragraph of the description at column 1. More specifically, osmotic devices comprise a semipermeable wall, i.e., a wall formed from a material that is permeable to an external fluid present in the environment of use and substantially impermeable to drug. The wall surrounds a reservoir containing the drug for release.

Water must enter the osmotic device through the semipermeable membrane. The drug release is comparable with the water influx rate. In use, the water is continuously absorbed into a drug reservoir of a defined surface area, A, through a semipermeable membrane having a defined permeability coefficient, P, and a defined thickness, h. The absorbed water dissolves the drug (the drug and/or osmotic salt having a defined saturation solubility, S), to create an osmotic pressure gradient ($p_s - p_e$) which pumps out dissolved drug at a rate of Q/t (cumulative amount released in time t):

$$Q/t = (P.A/h)\,(p_s - p_e)\,S$$

Since P, A and h are constants for any single osmotic device and S is constant for any single drug, Q/t (release rate) will be directly proportional to the osmotic pressure gradient ($p_s - p_e$), which, in turn, is constant as long as sufficient drug remains in the reservoir to maintain saturation solubility of the drug in the reservoir. Thus, osmotic devices require ingress of exterior fluid to dissolve drug/osmotic salts in order to create an osmotic pressure gradient that acts as a driving force to pump out drug from the reservoir. In summary, drug release from an osmotic device is osmotically driven and requires the external wall to be semipermeable (to ingress of water, but not to exit of the drug). A copy of page 534 of Physical Pharmacy by Alfred Martin published by Lea & Febiger (1993) describing the operation of an osmotic pump is provided herewith for the Examiner's convenience.

In contrast, for the intravaginal drug delivery devices of the present invention, there is no requirement for ingress of exterior fluid. Instead, dissolved drug is released via diffusion along a concentration gradient within the reservoir polymer. In addition, the sheath

discontinuously surrounding the reservoir is not semi-permeable, because drug can pass through the sheath (just at a low rate, hence the need for at least one hole or opening) to increase the rate of drug release from the intravaginal drug delivery devices of the present invention. In summary, drug release from the intravaginal drug delivery devices of the present invention is diffusion driven, rather than osmotically driven, as is the case for the devices of Theeuwes.

As already mentioned, osmotic devices function by external fluid in the environment of use being imbibed though the wall into the reservoir in a tendancy towards osmotic equilibrium at a rate determined by the permeability of the wall and the osmotic pressure building to cross the wall, see, for example, column 2, lines 65 to column 3, line 7 of Theeuwes.

It will be appreciated that, in the environment of use within the human or animal body, the external fluid is aqueous in nature, so that it is water, as the external fluid, that is being imbibed through the semipermeable wall.

From this, it will be appreciated that the Theeuwes reservoir must contain a material that attracts water, in other words, a hydrophilic material.

It is noted that the Examiner has drawn attention to the list of microporous materials at column 9, lines 19-21, which includes hydrophobic homopolymers, copolymers or interpolymers having a reduced bulk density.

Applicants respectfully submit that, in the external environment of the vagina, the incorporation of hydrophobic homopolymers, copolymers or interpolymers having a reduced bulk density in such an osmotic device would prevent imbibing of water through the wall into the reservoir and, thereby, prevent release of drug from such a device. Applicants, thereby, respectfully submit that the inclusion of such hydrophobic polymers in the list of suitable

reservoir microporous materials for an osmotic device would be understood by a man skilled in the art to be incorrect.

Applicants, therefore, respectfully submit that Theeuwes would not have disclosed, to a person of ordinary skill, that the reservoir of an osmotic device can contain a hydrophobic elastomeric polymer. In fact, the whole teaching of Theeuwes points towards the polymer being a hydrophilic polymer.

Zaffaroni concerns itself with microporous drug delivery devices. The Examiner suggests that Examples 1, 16 and 18 relate to an intravaginal drug delivery device. Applicants respectfully submit that Example 1 relates to an implant device. Example 1 does not implicitly or explicitly indicate the purpose of the implant device. Example 16 relates to an intrauterine device and Example 18 relates to a vaginal ring, illustrated in Figure 8. Zaffaroni concerns itself with a device whose wall comprises at least in part a microporous material, the pores of which contain a drug release rate controlling medium permeable to the passage of the drug (see column 1, lines 22-25; column 1, lines 31-34; column 3, lines 50-55; column 3, lines 63-65; column 4, lines 53-55; column 4, line 67 to column 5, line 3; column 7, lines 45-52; and column 8, lines 21-25). The reservoir of Zaffaroni is defined at column 13, line 64 to column 14, line 6 as being an inorganic or organic solid, of naturally occurring or synthetic origin.

The sheath of the present invention is required to discontinuously surround the at least one reservoir so as to define at least one hole or opening extending through the sheath to the at least one reservoir. The wall of Zaffaroni is formed of a microporous material, the micropores of which contain a drug release rate controlling medium. The passage at column 9, line 15 to 62 and at column 10, lines 32-38 teach that the radius of the micropores should be no more than 10

times larger than the molecular radius of the drug molecule and, ideally, the radius of the micropores should be about 2 to 3 times the molecular radius of the drug molecule. Zaffaroni goes on to teach, at column 10, lines 32-37, that a pore size of about 10 angstroms (0.000001mm) to 100 microns (0.1mm) can be suitably employed. The teaching of Zaffaroni does not encourage a skilled reader to consider providing at least one hole or opening in a sheath, having regard to the teaching at column 9 that the radius of the micropores should be no more than 10 times larger than the molecular radius of the drug molecule itself. There is, therefore, no incentive to modify the micropores containing drug release controlling material and replace them with at least one hole or opening, as required by the claims of the present invention.

Applicants conclude that Theeuwes and Zaffaroni do not render the subject-matter of Claims 1, 3, 6-8, 13-15 and 17 obvious.

Claim 4 has been rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Theeuwes, in view of Zaffaroni, and in further view of U.S. Patent No. 3,924,622 (Brooke).

With respect to Claim 4, Theeuwes, in view of Zaffaroni, fails to expressly disclose that the at least one hole or opening is in the shape of a slit. While Figures 3 and 4 of Brooke illustrate an intravaginal ring containing a drug that can defuse through a slot 65, column 1, lines 52-56 teach that the drug is dispensed by dissolution or vaporisation within the device into the fluid medium that enters through the slot, followed by diffusion of the dissolved or vaporised solid outwardly through the slot. Column 3, line 29 to column 4, line 13 teaches that the rate of diffusion of the drug substance to the slot is inversely proportional to the distance separating the drug surface from the slot and directly proportional to the area of the drug surface.

Brooke teaches that the cavity can be filled flush with slot 20 with a single pellet of drug substance, following which the drug is dissolved and medium diffuses into the cavity to replace the dissolved drug. Brooke teaches, as an alternative, that the cavity be only partially filled and, if this option is employed, the surface of the drug substance should be arcuate in contour (see column 3, lines 24-28). As the Examiner acknowledges, Brooke does not disclose an intravaginal drug delivery device comprising at least one reservoir containing at least one pharmacologically active agent or a prodrug thereof dispersed in a hydrophobic elastomeric polymer. The teaching of Brooke does not remedy the deficiency of one or both of Theeuwes and Zaffaroni. We respectfully submit that the subject-matter of Claim 4 is not obvious.

Claims 5, 9, 11 and 12 have been rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Theeuwes, in view of Zaffaroni, and in further view of U.S. Patent No. 2,962,023 (Chappaz et al.).

Theeuwes discloses a semipermeable wall that is permeable to external fluid and substantially impermeable to drug (see column 9, lines 55-57) but fails to teach the exact size and shape of the required at least one hole or opening in the sheath. Chappaz discloses a medicator having walls of solid material, usually a plastic substance (see column 1, lines 56 and 67). Useful wall (or sheath) materials are described at column 2, lines 16-22. The wall 10 has perforations 12 that are described in Example I as being small holes of about 0.03125 inch in diameter (0.79375mm in diameter). The Chappaz medicator contains a reservoir or depot supply of medicament enclosed within the hollow interior of the wall (or sheath). The medicator of Example I is filled with a medicating cream (see column 4, lines 8-9) that melts at body temperature and exudes slowly but continuously through the perforations 12. Example I goes on

to teach, at column 4, lines 19-21, that various medicaments such as creams, jellies, liquids or even powder may be enclosed within the hollow cavity of the medicator.

It will be appreciated that Chappaz does not disclose or suggest that the reservoir contain at least one pharmacologically active agent or a prodrug thereof dispersed in a hydrophobic elastomeric polymer.

Example II of Chappaz is a medicator filled with a vaginal jelly comprising a gelatine base modified to jelly consistency with glycerine and water. Again, Example II of Chappaz does not disclose or suggest that the reservoir contain at least one pharmacologically active agent or a prodrug thereof dispersed in a hydrophobic elastomeric polymer.

Applicants respectfully submit that the subject-matter of Claims 5, 9, 11 and 12 are not obvious over Theeuwes, in view of Zaffaroni and further in view of Chappaz.

Claim 10 has been rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Theeuwes, in view of Zaffaroni, and in further view of Chappaz, and further in view of U.S. Patent No. 4,014,987 (Heller et al.).

Figure 8 of Heller illustrates a hollow cervical tubular body for administering drug in the cervical canal. Heller concerns itself with drug release through bioerosion. More specifically, the Heller device comprises a body of erodable release rate controlling material containing the drug dispersed therethrough. The preferred release rate controlling material is hydrophobic poly (carboxylic acid) (see column 1, lines 63-67). The body of hydrophobic poly (carboxylic acid) bioerodes and gradually releases drug over a period of time (see column 2, line 1; column 2, line 16; column 3, line 57; column 11, lines 2, 12). Heller does not disclose or suggest employing hydrophobic elastomeric polymers in the reservoir. In addition, Heller does

not disclose or suggest a drug delivery device that is diffusion controlled, because Heller concerns itself solely with bioerosion as a control mechanism.

Applicants respectfully submit that Claim 10 is not obvious over Theeuwes, in view of Zaffaroni, and further in view of Chappaz and further in view of Heller.

Claim 16 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over Theeuwes, in view of Zaffaroni, and in further view of U.S. Patent No. 4,359,046 (Shaw Jr.).

As the Examiner acknowledges, Theeuwes in view of Zaffaroni fails to disclose a sheath comprising at least one additional pharmacologically active agent. Shaw, Jr. discloses medicated intrauterine devices, whose reservoir or body are fabricated from, for example, polyethylene (see column 4, line 63) or from low density polyethylene or polyethyl vinyl acetate (see column 11, lines 37-40). Shaw, Jr. fails to disclose that the sheath discontinuously surrounds the at least one reservoir so as to define at least one hole or opening extending through the sheath to the at least one reservoir. Applicants respectfully submit that Claim 16 is not obvious over Theeuwes in view of Zaffaroni and further in view of Shaw, Jr.

Claim 18 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over Theeuwes, in view of Zaffaroni, and in further view of U.S. Patent No. 6,394,094 (McKenna et al.).

With respect to Claim 18, which is directed to a method of manufacturing an intravaginal drug delivery device as is claimed in Claim 1, the Examiner will appreciate that Claim 1 has now been amended to incorporate the limitation of Claim 2 and, accordingly, this change obviates the obviousness rejection based on Zaffaroni in view of McKenna. For completeness, Applicant provides comments on McKenna as follows. McKenna concerns the manufacture of a drug delivery device by injection moulding. However, McKenna, as the

Examiner acknowledges, injects or extrudes a reservoir material into a hollow sheath in order to obtain a sheath that has a substantially uniform thickness. More specifically, at column 8, lines 35-37, it is taught that a membrane thickness uniformity of plus/minus 1% is achieved. Nowhere in McKenna is it disclosed, or even contemplated, that the sheath would merely discontinuously surround the at least one reservoir so as to define at least one hole or opening extending to the sheath through the at least one reservoir. Instead, McKenna concentrates on achieving, by extrusion, a substantially uniform sheath thickness, as has been identified by the Examiner.

Applicants respectfully submit that the subject-matter of Claim 18 is not obvious over Zaffaroni in view of McKenna.

This Amendment After Final Action is believed clearly to place this application in condition for allowance and, therefore, its entry is believed proper under 37 C.F.R. § 1.116. Accordingly, entry of this Amendment After Final Action, as an earnest effort to advance prosecution and reduce the number of issues, is respectfully requested. Should the Examiner believe that issues remain outstanding, it is respectfully requested that the Examiner contact Applicants' undersigned attorney in an effort to resolve such issues and advance the case to issue.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our address given below.

Respectfully submitted,

/Raymond R. Mandra/
Attorney for Applicants
Raymond R. Mandra
Reg. No. 34,382

FITZPATRICK, CELLA, HARPER & SCINTO
30 Rockefeller Plaza
New York, New York 10112-3801
Facsimile: (212) 218-2200

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include methylcellulose, sodium alginate, and other gel-forming materials. The drug diffuses from the viscous gel, and the release rate can be controlled by the degree of polymerization of the carrier and the ratio of drug to carrier. Wilson and Cuff[102] found that the optimum hydrogel concentration for sustained release of isomazole, an orally active cardiotonic, was 40 to 42%. Hydrophobic and digestible carriers include glycerides, waxes, fatty alcohols, and fatty acids. They constitute eroding tablets in which the release is achieved when the surface layer is continuously eroded by the GI fluids. Matrix tablets consist of insoluble and nondigestible materials, such as polyethylene, some waxes, and polyvinylchloride. The diffusion of a drug through this kind of matrix has been discussed in Chapter 13, pages 335 to 337. The kinetics of release is a function of the square root of time, and the release rate can be controlled by the tablet porosity, addition of soluble solids, and the ratio of drug to carrier.

Jambhekar and Cobby[103] prepared slow-release tablets using a polyvinylchloride–polyoxyethylene (PVC–PE) matrix and sodium salicylate as a model drug. The in vitro release of drug from a cylindrical PVC–PE matrix when all surfaces of the tablet are exposed to the dissolution fluid is described in the following equation:

$$f_t = (q + 2)K_r(t^{1/2} - t_o^{1/2}) - (2q + 1)[K_r(t^{1/2} - t_o^{1/2})]^2 + q[K_r(t^{1/2} - t_o^{1/2})]^3 \qquad (19-49)$$

where f_t is the fraction of drug released at time t, q is the ratio of tablet diameter to thickness, K_r is the rate constant, and t_o is the lag time. The rate constant, as well as the lag time, can be computed by fitting the fraction of drug released f_t to the cubic expression, equation (19–49), using a NONLIN program. Once k_r and t_o are known, the values of f_t at any time can be estimated.

Example 19–15. Compute the fraction released at 25° C of salicylate from insoluble matrices at 4:1 and 9:1 matrix-drug ratios and at t = 9 hours. The dissolution rate constants are K_r = 0.116 $hr.^{-1/2}$ and 0.101 $hr.^{-1/2}$; the lag times are $t_o^{1/2}$ = 0.341 $hr.^{1/2}$ and = 0.276 $hr.^{1/2}$. The ratio of tablet diameter to thickness in both cases is q = 2.84. For a matrix:drug ratio of 4:1, the fractional drug release is

$$f_t = (2.84 + 2)0.116(9.0^{1/2} - 0.341) - (2 \times 2.84 + 1)[0.116(9^{1/2} - 0.341)]^2 + 2.84[0.116(9^{1/2} - 0.341)]^3 = 0.941$$

For the matrix:drug ratio of 9:1,

$$f_t = (2.84 + 2)0.101(9.0^{1/2} - 0.276) - (2 \times 2.84 + 1)[0.101(9^{1/2} - 0.276)]^2 + 2.84[0.101(9^{1/2} - 0.276)]^3 = 0.885$$

Note that the fraction released depends on the matrix:drug ratio. The larger the ratio, the smaller the fraction released. Jambhekar and Cobby[103] showed that the release constant from this type of matrix was independent of the pH of the dissolution fluid and the flow rate of the fluid past the tablet, so that the in vivo behavior may be less subject to variations in the GI tract.

Osmotic Pump. The *elementary osmotic pump,* also known as Oros or Gastrointestinal Therapeutic System, was first described by Theeuwes and Yum and was introduced by Alza Corporation.[104] The dosage form has a semipermeable membrane on one surface to bring water by osmosis into the drug reservoir in the tablet. The device is shown in Figure 19–17(a). The hydrostatic pressure generated by the influx of water forces the release of a saturated solution of the drug through an opening in the tablet, as seen in Figure 19–17(b). The rate of drug release is constant (zero-order) until the excess undissolved drug is depleted. The release rate then decreases parabolically to zero (Fig. 19–18). Earlier sustained-release forms were markedly affected by physiologic pH changes. With the Oros system, the rates of release of phenobarbital, placed in both artificial gastric fluid at pH 2 and intestinal fluid at pH 7.5, were found to be independent of pH. The release rate of the device may be altered by changing the nature of the semipermeable membrane.

Sample Calculations. Theeuwes[105] first tested the elementary osmotic pump for drug delivery using potassium chloride to serve as both the osmotic agent and the drug model. In a later report, Theeuwes et al.[106] designed a therapeutic system, based on the principle of the osmotic pump, to deliver indomethacin

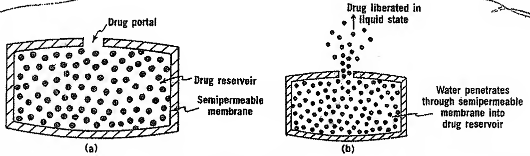

Fig. 19–17. The elementary osmotic pump, Oros (Alza), used as a gastrointestinal therapeutic system. The figure shows the liberation of the drug through the small orifice owing to osmosis of fluids through the semipermeable membrane and into the drug reservoir. (After K. Heilmann, *Therapeutic Systems*, Georg Thieme, Stuttgart, 1978, p. 49.; reproduced with permission of the copyright owner.)